Top Tips and Recommendations for Sodium Glucose Co-transporter 2 inhibitors (SGLT2i) in HFrEF

NHS Northern Treatment Advisory Group

Introduction and Purpose of Document

SGLT2 inhibitors are an established class of medications for the treatment of type 2 diabetes and act by preventing the absorption of glucose and sodium, mainly from the proximal renal tubule in the kidney. Glucose and sodium are, therefore, lost in urine resulting in a fall in blood glucose level, an osmotic diuresis, reduction in blood pressure and weight loss. These drugs have been licensed and used widely in people with T2DM and have shown significant cardiovascular and renal benefits in different subsets of this group of patients.

Cardiovascular outcome trials have shown this class of drug to be effective in reducing both morbidity and mortality from cardiovascular disease, as well as beneficial effects on Heart Failure with reduced ejection fraction (HFrEF) (e.g. reductions in risk of hospitalisation, risk of worsening heart failure and improvement in symptom scores). These effects are thought to be independent of their benefits in lowering blood glucose levels. The effects on heart failure are particularly impressive as they are present both in those with or without previous cardiovascular and/or chronic kidney disease, and also benefit those without diabetes.

Dapagliflozin and empagliflozin both have a NICE TA and are licensed for use in symptomatic chronic HFrEF in the UK.

This document has been developed for the use of an SGLT2 within its current licence for the treatment of HFrEF. The primary purpose of this guide is to ensure that, where an SGLT2 is prescribed in a person for HFrEF, it is undertaken safely. This can be achieved by ensuring that an SGLT2 is only prescribed for the appropriate patients and that the relevant information is given to patients to ensure safety.

Prescribing SGLT2 - Dapagliflozin or Empagliflozin in HFrEF

It is important to note each Trust may have their own SGLT2 in HF guidelines and processes depending on service set up and needs.
Therefore, this document is not exhaustive and should only be used as a guide/prompt.
It is also worth noting that ESC, American and Canadian guidelines and recommendations differ to those from NICE.

When to consider SGLT2 in HFrEF

NICE TA states SGLT2 in HFrEF should only be initiated by or on the advice of a heart failure specialist or Consultant Cardiologist
Consider dapagliflozin 10mg OD or empagliflozin 10mg OD if:

- Patient symptomatic secondary to chronic heart failure with reduced ejection fraction and already optimised on standard heart failure treatment *(clinical judgement should be applied when assessing if a patient is optimised on therapy)*
  - *Standard care is defined by NICE as:*
    - *angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers, and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or*
    - *sacubitril valsartan, with beta blockers, and, if tolerated, MRAs*
- EF ≤ 40%
- eGFR ≥ 15ml/min for dapagliflozin or
- eGFR ≥ 20ml/min for empagliflozin (see dosing table below for further information)
- NYHA II-IV

Use with CAUTION in the following situations:

- Patient Characteristics
  - Body mass index <25 kg/m² (<23 kg/m² in South Asian patients)
  - Person adhering to a ketogenic/low calorie/low carbohydrate diet (20-50g/day of carbohydrate or less than 10% of a 2000 kcal/day diet)
  - Recent weight loss
  - Potential for pregnancy
  - People at risk of hypotension/hypovolaemia (e.g. on diuretic and/or multiple antihypertensive therapies, elderly)
  - People diagnosed with or at risk of frailty
  - Cognitive impairment or use of medication compliance aid (as this *may* imply inadequate understanding required to follow sick day rules and take action to prevent and identify DKA)
- Other Past Medical History
  - On long term or recurrent courses of steroids
  - Raised haematocrit
  - Severe hepatic impairment
  - Recurrent urinary or genital tract infections
- Diabetes History
  - Long duration of diabetes (generally over 10 years from diagnosis)
  - Person with very high level of HbA1c >86 mmol/mol
  - Person considered at high risk of acute effects of hyperglycaemia (e.g. dehydration due to non-adherence to medication)
  - Active foot disease and past history of active foot disease/foot ulceration – consider discussion with specialist, ensure regular preventative footcare
  - Existing diabetic foot ulcers
  - Previous lower limb amputation
  - History of peripheral arterial disease (PAD)
  - **Taking sulphonylureas and/or insulin – increased risk of hypoglycaemia if commenced on SGLT2**

CONTRAINDICATIONS - AVOID in the following situations:

- Patient Characteristics
  - Age <18 years
  - Pregnant, breastfeeding, female in their child-bearing years and sexually active without contraception
  - Person with excess alcohol consumption or IVDU
  - History of allergic reaction to dapagliflozin or empagliflozin or any of their excipients
  - eGFR < 15 ml/min for dapagliflozin or < 20ml/min for empagliflozin
- Current Medical History
  - Acutely unwell person (acute medical illness including COVID-19, surgery or planned medical procedure)
  - Active foot disease
  - Inpatient with acute vascular event who is not stable
  - Eating disorder
  - eGFR outside than allowed in the up-to-date licensing of the medication being considered
  - Already on SGLT2 inhibitor for other co-morbidity
  - Organ transplant
  - Patients receiving dialysis
- Diabetes History
  - Suspected or possible T1DM
  - Any diagnosis or suspicion of latent autoimmune diabetes (LADA), other genetic causes of diabetes, known pancreatic disease or injury, or people who rapidly progressed to needing insulin within 1 year of diagnosis
  - Past history of diabetic ketoacidosis

SGLT2 in HFrEF Dosing

SGLT2 Inhibitor	Dose *(When using in HFrEF)*	Dose Adjustments *(When using in HFrEF)*					
		eGFR > 60	eGFR 45-59	eGFR 31-44	eGFR 15-30	eGFR <15	Hepatic Impairment
Dapagliflozin PIL/SPC	10mg once daily. With or without food.	Initiate 10mg once daily.				**Do not initiate if eGFR <15ml/min/1.73m²**	No dose adjustment is necessary for patients with mild or moderate hepatic impairment. Use with caution in severe impairment (risk of increased exposure). See SPC for further information.
		eGFR > 60	eGFR 45-59	eGFR 31-44	eGFR 20-30	eGFR <20	
Empagliflozin PIL/SPC	10mg once daily. With or without food.	Initiate 10mg once daily.				**Do not initiate and discontinue if already taking if eGFR <20ml/min/1.73m²**	

Patient Education – Sick Day Rules

All patients should be counselled on initiation of SGLT2 for HFrEF (by the initiating clinician) about sick day rules and when to stop taking their SGLT2 due to associated risks with dehydration and development of DKA.

- If ill with diarrhoea, UTI, vomiting, fever or unusual drowsiness, patient's should be advised to STOP SGLT2 and don't restart until feeling better and eating/drinking fluids normally
  - Restart only AFTER patient has been eating normally for AT LEAST 24 HOURS AND no longer acutely unwell
- Encourage patient to avoid dehydration with appropriate fluid intake
  - Unless advised to restrict fluids, such as patients with HF. This may require discussion with HF specialist team to consider temporarily relaxing fluid restriction/increasing fluid intake
- ALL patients must be counselled on the risk of ketoacidosis and signs and symptoms of this (nausea, vomiting, abdominal pain, stupor, fatigue, difficulty breathing) and to STOP SGLT2 inhibitor if any symptoms develop
- To seek urgent medical attention if symptoms of Fournier's gangrene (e.g. severe pain, tenderness, erythema, swelling in genital or perineal area)
- Seek medical advice if particularly unwell with infection or illness
- Stop SGLT2 prior to surgery–as advised by pre-op team

Side Effects

Common:

- Increased risk of UTI
- Polydipsia
- Polyuria
- Urinary disorders
- Fungal genital infections
- Volume depletion effects (thirst, postural dizziness, hypotension, dehydration)
- Hypoglycaemia (increased risk if on sulphonylureas and/or insulin)
- Decreased eGFR

Uncommon but **serious**: (see MHRA alerts below for more information)

- DKA
- Fournier's Gangrene
- Lower limb amputation – encourage regular preventative footcare

Please see individual drug monographs in BNF/SPC for a complete side-effect profile – see hyperlink in table overleaf.

Monitoring Requirements and Documentation

- Additional monitoring after starting SGLT2 inhibitors is NOT required. Routine monitoring of kidney function should continue as part of routine care, frequency guided by national and local guidance HF as appropriate, but additional routine tests are not required after starting SGLT2 therapy.
- It must be clearly documented on the patient's medical record that the indication for SGLT2 is HFrEF and not T2DM or CKD to ensure follow up and monitoring is appropriate. However it should be noted some patients may have multiple co-morbidities for which SGLT2 therapy will confer benefit.
- It is worth noting that due to its mechanism of action patients on an SGLT2 will test positive for glucose in their urine
- Patients with T2DM who are commenced on SGLT2 for HF may require adjustment to their other glucose lowering medication and closer monitoring of HbA1c/capillary blood glucose following initiation of SGLT2 due to the potential for hypoglycaemia. This should be considered and advised by the specialist team initiating the SGLT2.

Contacts and Communication Links – HF Teams in Secondary Care

It is important to note each Trust may have their own SGLT2 in HF guidelines and processes depending on service set up and needs. Therefore, this document is not exhaustive and should only be used as a guide/prompt. Any further queries relating to patients prescribed SGLT2 for HF should be referred to the relative team below:

Gateshead Health NHS Foundation Trust: Hamza Khalil, Advanced Specialist Pharmacist, Heart Failure, hamza.khalil1@nhs.net
Claire Davies, Diabetes and Endocrinology Specialist Pharmacist, claire.davies62@nhs.net
Newcastle upon Tyne NHS Foundation Trust: Dr Kristian Bailey, Consultant Cardiologist, kristian.bailey2@nhs.net
Northumbria Healthcare NHS Foundation Trust: Alastair Green, Senior Clinical Pharmacist - Cardiology, Alastair.green@northumbria-healthcare.nhs.uk
North Cumbria Integrated Care NHS Foundation Trust, West Cumberland Hospital (WCH) Heart Failure Team: 07824 351769, Cumberland Infirmary Heart Failure Team: 07824 383884
South Tyneside and Sunderland NHS Foundation Trust: stsft.sunderlandheartfailureteam@nhs.net

For other Trusts please use usual referral/advice and guidance processes for further advice.

Additional Important Safety Information

Additional Important safety information – Please see hyperlinks for more detailed advice:

- MHRA/CHM advice (updated April 2016): SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis (DKA)
  - People should be informed on the signs and symptoms of DKA, discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
  - Test for raised ketones in patients with ketoacidosis symptoms, even if plasma glucose levels are near-normal
- MHRA/CHM advice (MHRA/CHM advice March 2017): SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)
  - SGLT2i's may increase the risk of lower-limb amputation (mainly toes). All people taking an SGLT2i should be counselled on good preventive foot care. Review if lower limb complications develop (e.g. skin ulcer, osteomyelitis, or gangrene). Monitor people with risk factors for amputation.
- MHRA/CHM advice: SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) (February 2019)
  - If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required)
  - Fournier's gangrene is a rate but potentially life-threatening infection that requires urgent medical attention
- MHRA/CHM advice: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness (March 2020)
  - SGLT2 inhibitor treatment should be interrupted in people who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when the ketone values are normal and the person's condition has stabilised
- MHRA/CHM advice: Dapagliflozin (Forxiga): no longer authorised for treatment of type 1 diabetes mellitus
  - The authorisation holder for dapagliflozin has withdrawn the indication for type 1 diabetes mellitus. The removal of the type 1 diabetes indication is not due to any new safety concerns and the other indications of dapagliflozin are unchanged

Further Information and References

- Summary of Product Characteristics (SPC) for dapagliflozin available at: www.medicines.org.uk
- NICE Dapagliflozin for treating chronic heart failure with reduced ejection fraction Technology appraisal guidance [TA679] available at: https://www.nice.org.uk/guidance/TA679
- NICE Empagliflozin for treating chronic heart failure with reduced ejection fraction Technology appraisal guidance [TA773] available at: https://www.nice.org.uk/guidance/ta773

Produced by Claire Davies and Hamza Khalil and North East and North Cumbria HF Network, June 2022, for review June 2023

For any queries/feedback please contact: claire.davies62@nhs.net and hamza.khalil1@nhs.net